PCT/GB01/04345

CLAIMS

1. A compound of formula (I):

wherein:

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R¹ represents C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkynyl-Y¹-, aryl-Y¹-, heteroaryl-Y¹-, aryl-(O)_t-aryl-Y¹-, aryl-(O)_t-heteroaryl-Y¹-, heteroaryl-(O)_t-aryl-Y¹-, heteroaryl-O-Y¹-, heteroaryl-O-Y¹-, heteroaryl-O-Y¹-, C₂₋₆ alkenyl-Y¹-, aryl-O-Y¹-, heteroaryl-O-Y¹-, C₁₋₆ alkyl-SO₂-Y¹-, M-Y¹-, J²-Y¹-, -CN or C₃₋₈ cycloalkyl-Y¹- or C₃₋₈ cycloalkenyl-Y¹-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C₁₋₆ alkyl groups;

10 R² represents hydrogen or C₁₋₆ alkyl;

X represents ethylene or a group of formula CR^eR' wherein R^e and R' independently represent hydrogen or C_{1-4} alkyl or R^e and R' may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R³ and R⁴ independently represent hydrogen or C₁₋₄ alkyl;

Z represents a bond, CO, SO₂, CR⁹R⁶(CH₂)_n, (CH₂)_nCR⁹R⁶, CHR⁶(CH₂)_nO, CHR⁶(CH₂)_nS, CHR⁶(CH₂)_nOCO, CHR⁶(CH₂)_nCO, COCHR⁶(CH₂)_n or SO₂CHR⁶(CH₂)_n;

 R^5 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl- C_{2-6} alkenyl- or a group of formula $-Y^2-J^1$:

R⁶ represents hydrogen, C₁₋₄ alkyl, CONR⁷R⁸ or COOC₁₋₆ alkyl;

a and b represent 1 or 2, such that a+b represents 2 or 3;

n represents an integer from 0 to 4;

J¹ and J² independently represent a mojety of formula (K):

$$X^1$$
 X^2
 (K)

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wherein X¹ represents oxygen, NR¹³ or sulphur, X² represents CH₂, oxygen, NR¹⁰ or sulphur, m¹ represents an integer from 1 to 3 and m² represents an integer from 1 to 3, provided that m¹+m² is in the range from 3 to 5, also provided that when both X¹ and X² represent oxygen, NR¹³, NR¹⁰ or sulphur, m¹ and m² must both not equal less than 2, wherein K is optionally substituted by one or more -Y³-aryl, -Y³-heteroaryl, -Y³-CO-aryl, -COC₃-gcycloalkyl, -Y³-CO-heteroaryl, -C¹-g alkyl, -Y³-COOC¹-g alkyl, -Y³-COC¹-g alkyl, -Y³-W, -Y³-CO-W, -Y³-NR¹¹R¹², -Y³-CONR¹¹R¹², hydroxy, oxo, -Y³-SO₂NR¹¹R¹², -Y³-SO₂C¹-g alkyl, -Y³-SO₂aryl, -Y³-SO₂heteroaryl, -Y³-NR¹⁴CONR¹¹R¹² alkyl, -Y³-NR¹⁴SO₂C¹-g alkyl, -Y³-NR¹⁴CONR¹¹R¹², -Y³-NR¹²CONR¹¹R¹², -Y³-NR¹²CONR¹²R¹², -Y³-NR¹²CONR¹²R¹²

R⁷, R⁸, R⁹, R¹⁰, R¹³, R¹⁴ and R¹⁵ independently represent hydrogen or C₁₋₆ alkyl;

R¹¹ and R¹² independently represent hydrogen or C₁₋₆ alkyl or R¹¹ and R¹² together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

M represents a C_{3-8} cycloalkyl or a C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-8} alkyl, halogen or hydroxy groups;

t represents 0 or 1.

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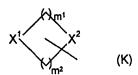
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Y¹, Y² and Y³ independently represent a bond or a group of formula –(CH₂)_pCR^cR^d(CH₂)_q-wherein R^c and R^d independently represent hydrogen or C₁₋₄ alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C₃₋₈ cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5; and salts and solvates thereof.

2. A compound of formula (I) according to claim 1 wherein R^1 -represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} alkynyl, C_{2-6} alkynyl, C_{2-6} alkynyl- Y^1 -, aryl- Y^1 -, heteroaryl- Y^1 -, Y^1 -, heteroaryl- Y^1 -, Y^1 -, Y^1 -, or Y^1 -, heteroaryl- Y^1 -, Y^1 -, or Y^1 -, heteroaryl- Y^1 -, Y^1 -, or Y^1 -,

J¹ represents a moiety of formula (K):



wherein X¹ represents oxygen, NR¹³ or sulphur, X² represents CH₂, oxygen, NR¹⁰ or sulphur, m¹ represents an integer from 1 to 3 and m² represents an integer from 1 to 3, provided that m¹+m² is in the range from 3 to 5, also provided that when both X¹ and X² represent oxygen, NR¹³, NR¹⁰ or sulphur, m¹ and m² must both not equal less than 2, wherein K is optionally substituted by one or more -Y³-aryl, -Y³-heteroaryl, -Y³-CO-aryl, -Y³-CO-heteroaryl, -C₁-β alkyl, -Y³-COC1-β alkyl, -Y³-W, -Y³-CO-W, -Y³-NR¹¹R¹², -Y³-CONR¹¹R¹², hydroxy, oxo, -Y³-SO₂NR¹¹R¹², -Y³-SO₂C1-β alkyl, -Y³-SO₂aryl, -Y³-SO₂heteroaryl, -Y³-NR¹⁴C1-β alkyl, -Y³-NR¹⁴SO₂C1-β alkyl, -Y³-NR¹⁴COOR¹⁵ or -Y³-OCONR¹¹R¹² groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

3. A compound of formula (I) according to claim 1 wherein R^1 represents C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl- Y^1 -, heteroaryl- Y^1 -, aryl- $(O)_t$ -aryl- Y^1 -, aryl- $(O)_t$ -heteroaryl- Y^1 -, heteroaryl- Y^1 -, Y^1 -, Y^1 -, heteroaryl- Y^1 -, Y^1 -, Y^1 -, Y^1 -, heteroaryl- Y^1 -, Y^1 -,

Z represents a bond, CO, CR⁹R⁶(CH₂)_n, CHR⁶(CH₂)_nO, CHR⁶(CH₂)_nS, CHR⁶(CH₂)_nOCO, CHR⁶(CH₂)_nCO; and

J¹ represents a moiety of formula (K):

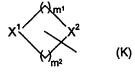
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wherein X¹ represents oxygen, nitrogen, NR¹³ or sulphur, X² represents CH₂, oxygen, nitrogen, NR¹⁰ or sulphur, m¹ represents an integer from 1 to 3, m² represents an integer from 1 to 3, provided that m¹+m² is in the range from 3 to 5, also provided that when X² represents oxygen, nitrogen, NR¹⁰ or sulphur, m¹and m² must both not equal less than 2, wherein K is optionally substituted by one or more -Y³-aryl, -Y³-heteroaryl, -Y³-CO-aryl, -Y³-CO-heteroaryl, -C₁-a alkyl, -Y³-COCC₁-a alkyl, -Y³-COC-a alkyl, -Y³-CO-W, -Y³-NR¹¹R¹², -Y³-CONR¹¹R¹², hydroxy, oxo, -Y³-SO₂NR¹¹R¹², -Y³-SO₂C₁-a alkyl, -Y³-SO₂aryl, -Y³-SO₂heteroaryl, -Y³-NR¹⁴SO₂C₁-a alkyl, -Y³-NR¹⁴CONR¹¹R¹², -Y³-

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NR¹⁴COOR¹⁵ or -Y³-OCONR¹¹R¹² groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

- 4. A compound of formula (I) according to any one of claims 1 to 3 wherein R¹ represents aryl-Y¹-.
- 5. A compound of formula (I) according to claim 4 wherein R¹ represents optionally substituted phenyl-Y¹- in which phenyl may be optionally substituted.
 - 6. A compound of formula (I) according to any one of claims 1 to 5 wherein Y¹ represents -CH₂-.
 - 7. A compound of formula (I) according to claim 1 wherein X represents methylene.
- 10 8. A compound of formula (I) according to claim 1 wherein a and b both represent 1.
 - 9. A compound of formula (I) according to claim 1 or claim 3 wherein Z represents a bond, CO, CHR⁶(CH₂)_n, CHR⁶(CH₂)_nO or CHR⁶(CH₂)_nCO.
 - 10. A compound of formula (I) according to claim 9 wherein Z represents CH₂.

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- 11. A compound of formula (I) according to claim 1 wherein R⁶ represents phenyl optionally substituted with one or more halogen atoms.
 - 12. A compound of formula (I) according to claim 11 wherein R⁶ represents 3,4-dichlorophenyl.
 - 13. A compound of formula (I) according to any one of claims 1 to 12 as described in Examples 1 to 240 or a salt or solvate of any one thereof.
- 20 14. A compound of formula (I) according to claim 13 which is 2-[3(Aminosulfonyl)phenyl]-N-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}acetamide or a solvate thereof.
 - 15. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.
 - 16. A compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.
 - 17. Use of a compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of inflammatory diseases.
 - 18. A method of treatment or prophylaxis of inflammatory diseases eg. asthma which comprises administering to a patient an effective amount of a compound of formula (I) as defined in any one of claims 1 to 14 or a pharmaceutically acceptable salt or solvate thereof.

- 19. A process for preparing a compound of formula (I) according to any one of claims 1 to 14 which comprises:
- (a) acylation of a compound of formula (II)

$$\begin{array}{c|c}
H & X & O \\
\downarrow & & \downarrow \\
R^2 & (\downarrow)_a & R^4
\end{array}$$

$$\begin{array}{c}
\downarrow & & \\
\downarrow$$

- wherein R², R³, R⁴, R⁵, X, Z, a and b are as defined in claim 1, with a compound of formula R¹COOH or an activated derivative thereof, wherein R¹ is as defined in claim 1; or
 - (b) reacting a compound of formula (III)

wherein R¹, R², R³, R⁴, X, a and b are as defined in claim 1, with a compound of formula

10 L¹-Z-R⁵, wherein Z and R⁵ are as defined in claim 1 and L¹ represents a suitable leaving group; or

- (c) deprotecting a compound of formula (I) which is protected; or
- (d) interconversion of other compounds of formula (i).
- 20. A process for preparing a compound of formula (I) according to any one of claims
 15 1 to 14 which comprises:
 - (e) forming a compound of formula (I) wherein R¹ represents heteroaryI-Y¹-, aryI-(O)t-heteroaryI-Y¹- or heteroaryI-(O)t-heteroaryI-Y¹- (wherein said Y¹ group is attached to heteroaryI via a heterocyclic nitrogen atom) and R² represents hydrogen which comprises reacting a compound of formula (IV)

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$$L^{2} \xrightarrow{V^{1}} X \xrightarrow{O} \xrightarrow{()_{b}} R^{3}$$

$$\downarrow Z$$

or a protected derivative thereof wherein R³, R⁴, R⁵, X, Y¹, Z, a and b are as defined in claim 1, L² represents a suitable leaving group, such as a halogen atom eg. bromine and P¹ represents a solid phase resin bound protecting group, with a heterocyclic compound defined by the R¹ groups heteroaryl, aryl-(O)_t-heteroaryl or heteroaryl-(O)_t-heteroaryl above wherein said heteroaryl group contains at least one NH atom, followed by removal of the solid phase resin bound protecting group; or

- (f) forming a compound of formula (I) wherein Z represents $CR^9R^6(CH_2)_n$ and R^9 represents hydrogen which comprises reacting a compound of formula (III) or a protected derivative thereof with a compound of formula $R^6CO(CH_2)_nR^5$, followed by reduction of the resultant imine; or
- (g) forming a compound of formula (I) wherein Z represents CO by reacting a compound of formula (III) or a protected derivative thereof with a compound of formula R⁵COOH or an activated derivative thereof.

15 21. A compound of formula (II)

wherein R², R³, R⁴, R⁵, X, Z, a and b are as defined in claim 1 or a protected derivative thereof, or a salt or solvate thereof.

22. A compound of formula (III)

wherein R^1 , R^2 , R^3 , R^4 , X, a and b are as defined in claim 1 or a protected derivative thereof, or a salt or solvate thereof.

23. A compound of formula (IV)

$$L^{2} \xrightarrow{Y^{1}} X \xrightarrow{O} (1)_{b} R^{3}$$

$$\downarrow Q \qquad \qquad \downarrow R^{4}$$

$$\downarrow Z \qquad \qquad \downarrow R^{5}$$

$$\downarrow Q \qquad \qquad \downarrow R^{4}$$

$$\downarrow Q \qquad \qquad \downarrow R^{5}$$

$$\downarrow Q \qquad \qquad \downarrow R^{5}$$

$$\downarrow Q \qquad \qquad \downarrow R^{5}$$

wherein R³, R⁴, R⁵, X, Y¹, Z, a and b are as defined in claim 1, L² represents a suitable leaving group, such as a halogen atom eg. bromine and P¹ represents a solid phase resin bound protecting group, or a salt or solvate thereof.